## REMARKS

Claims 10-30 are currently pending in this application. Claims 1-9 were cancelled by the Response to Restriction Requirement filed May 9, 2002, and Claims 31-38 are cancelled by the Amendment filed September 25, 2002. Claims 10-11 and 19-30 are being cancelled herewith. New Claim 39 is being added herewith. Support for this amendment can be found generally throughout the specification, and particularly original Claims 3-9 and Table 2 at page 33. Applicants are also amending herewith Table 2 of the specification to correct a typographical error. Applicants submit that this amendment does not introduce new matter. Applicants submit that entry of the present amendments is appropriate because applicants are filing concurrently herewith a Request for Continued Examination. Following entry of the foregoing amendments, Claims12-18 and 39 will be pending. Applicants respectfully request further examination of those claims.

**The Office Action:**

Claims 10-30 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to make or use the invention. Claims 10-30 were not rejected on the basis of any prior art. Applicants respectfully traverse the foregoing rejection.

**Amendment of the Specification:**

Applicants are amending herewith Table 2 at page 33 of the specification to correct a typographical error. The heading of the first column of the table is shown as "R". However, there is no substituent in the formula shown on page 21 of the specification designated as "R". Applicants are amending the heading of the first column in Table 2 to state that the

substituent is either $R_{h1}$ or $R_{h2}$. This amendment does not introduce new matter because it is clear to a person skilled in the art that the list of substituent shown in the first column are those listed in original claims 3-9 as being substituted at $R_{h1}$ or $R_{h2}$. Furthermore, the heading of the second column of Table 2 of the "$\alpha/\beta$ ratio at position 16" further indicates that the substitutions in the first column are at $R_{h1}$ or $R_{h2}$. Accordingly, applicants submit that entry of the amendment to the specification is appropriate because it does not introduce new matter, but, rather, merely corrects a typographical error that is clearly understood by a person skilled in the art.

**Rejection under 35 U.S.C. § 112, First Paragraph:**

Claims 10-30 were under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such as way as to enable one skilled in the art to make and use the invention. It is the Examiner's position that Claims 10-30 fail to meet the standards for enablement as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The Examiner specifically points to six of the eight factors *In re Wands* factors, and asserts that when they are weighed, one skilled in the art would be unable to practice this invention without undue experimentation. Applicants respectfully traverse this rejection for the reasons provided herein.

Applicants are canceling herewith Claims 10-11 and 19-30. In response to the Examiner's request, applicants are adding herewith new Claim 39, which incorporates the limitations of Claim 11 and adds a Markush group comprised of the selection of possible compounds for $R_{h1}$ and $R_{h2}$ taken from Claims 12-18. This amendment constitutes a substantial narrowing of the scope of the pending claims, as requested by the examiner. Applicant submits that, as amended, Claims 12-18 and 39 meet the requirements of 35 U.S.C. § 112.

1. The Nature of the Invention. The Examiner states in the Office Action that the claimed invention is drawn to a method of treating angiogenesis by 2-substituted estradiol derivatives of the formula in Claims 10 and 19.

Applicants respectfully maintain that Examiner's statement is moot in view of the foregoing amendments. The claimed invention is drawn to a method of treating angiogenesis comprising administering to an endothelial cell an angiogenesis inhibiting amount of an analog or derivative of 2-methoxyestradiol that is modified at the 16-carbon.

Applicants respectfully maintain that the Examiner's statement regarding the nature of the invention is incomplete and provides no basis for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph, as being non-enabled.

2. The State of the Prior Art. According to the December 2, 2002, Office Action, it is the Examiner's position that the prior art of record teaches a method of treatment of angiogenesis using, for example, 2-methoxy estradiol, 2-ethoxy estradiol, 2-alkoxyestradiol derivatives, and estrone, 2-hydroxyalkylestradiols, 2-methoxyoestrone-3-*O*-sulfamate. The Examiner states that all the compounds are estradiol or estrone derivatives known to treat angiogenesis or cancer.

Applicants respectfully maintain that the Examiner's statement provides no basis for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph as being non-enabled. Rather, Applicants note that if, as the Examiner states, estradiol or estrone derivatives are known to treat angiogenesis or cancer, any pharmaceutical formulations, any dosing schedules, or any other relevant information known regarding these derivatives would provide support for Claims 12-18 and 39 of the present invention being fully enabled, because such information would be available to one of ordinary skill at the time the invention was made.

Therefore, Applicants respectfully maintain that the Examiner's statement regarding derivatives known to treat angiogenesis or cancer provides no basis for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph, as being non-enabled, but rather supports their enablement.

3. The Predictability in the Art. As stated in the December 2, 2002, Office Action, it is the Examiner's position that there is a general lack of predictability in the pharmaceutical art, and the unpredictability of the steroid art is very high. The Examiner points to the following evidence.

a. *Applicants' Specification, page 20, lines 20-25 (Table 1).* It is the Examiner's position that the relative antiproliferative activities of 2-methylhydroxy estradiol, 2-formyl estradiol, and 2-acetyl estradiol presented in Table 1 (*see* specification, page 20) are indicative of the high unpredictability of the steroid art. The Examiner uses this antiproliferative data as support that method of Claims 10-30 fails to meet the standards for enablement as set forth in *In re Wands*. The Applicants respectfully traverse the Examiner's conclusion for the following reasons.

Table 1 (specification, page 20, lines 20-25) summarizes the results of three (3) different assays that are useful in determining and predicting the antiproliferative and antitumor activity of the compounds, namely the $IC_{50}$ values in HUVEC cells, the $IC_{50}$ values in MDA-MB-231 cells, and the Proliferation Index in estrogen dependant MCF-7 cells. As seen from these data, all of the 2-modified analogs presented in Table 1 have significantly lower estrogenic activity than estradiol, as indicated by the MCF-7 cell Proliferation Index. Further, all of these compounds exhibited antiproliferative or antitumor activity in at least one assay. Both the 2-methylhydroxy and 2-formyl derivatives had good antiproliferative activity in HUVEC cells, while the 2-acetyl E2 had good activity in breast tumor MDA-MB-231 cells. Therefore,

Applicants respectfully assert that Table 1 *supports* the enablement of Claims 10-30 by indicating what type of antiproliferative or antitumor activity to look for in screening the claimed compounds.

Accordingly, Applicants respectfully assert that the specification clearly and concisely indicates standard tests that allow rapid screening and identification of the claimed compounds that exhibit angiogenesis inhibiting activity. Therefore, Applicants respectfully maintain that Table 1 provides no basis or support for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled, but rather *supports* the enablement of Claims 10-30 by indicating what to look for.

b. *The Predictable Activity of the Compounds of Claims 10 and 19.* It is the Examiner's position that it is not obvious from the disclosure of one species what other species will work. In support of this position, the Examiner cites *In re Dreschfield* 110 F.2d 235, 45 USPQ 36 (CCPA 1940) for the general rule, "...in cases involving chemicals and chemical compounds, which differ radically in their properties, it must appear in an applicant's specification either by enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

Applicants respectfully maintain that the *In re Dreschfield* rule is not applicable to Applicants' Claims 12-18 and 39, and therefore cannot constitute a basis for an non-enablement rejection, for the following reasons. Applicants respectfully assert that the genus provided in Claim 39 does not encompass chemical compounds "which differ radically in their properties" according to *In re Dreschfield.* The claimed invention is drawn to a method of treating angiogenesis comprising administering an angiogenesis inhibiting amount of an analog or derivative of 2-methoxyestradiol that is modified at the 16-carbon. Ignoring stereoisomers, only

seven (7) different chemical compounds are represented by Claim 39, all of which are modified only at the 16-position. Applicants assert that these compounds do not constitute unrelated members of a Markush group, but rather are structurally and chemically related.

Further, even if the *In re Dreschfield* rule were applicable to Applicants' Claims 12-18 and 39, Applicants respectfully assert that Applicants's specification provides both: 1) enumeration of a sufficient number of the members of a group; and 2) other appropriate language indicating that the compounds included in the claims are capable of accomplishing the desired result. First, Claims 12-18 are each drawn to a single 16-substituted 2-methoxyestradiol compound, and Table 2 (Example 24, page 33) discloses the antiangiogenic and antitumor activity of each compound. Therefore, Applicants respectfully assert that by numerous examples *and* by appropriate language, the compounds encompassed by this invention capable of accomplishing the desired inhibition of angiogenesis are clearly enumerated.

Moreover, the specification suggests one reason, among others, why the compounds disclosed therein were selected for testing. Since 2-methoxyestradiol is metabolized to a much less active metabolite, the present invention adds steric bulk and/or modification of electrostatic characteristics at the 16-carbon of 2-methoxyestradiol for retarding or preventing interaction of 17β-hydroxysteroid dehydrogenases and co-factor $NADP^+$ on this substrate. Addition of steric bulk and/or modification of electrostatic characteristics at the 16-carbon of 2-methoxyestradiol may retard or prevent glucuronidation. It is believed that retardation or prevention of these two metabolic deactivation pathways prolongs the serum lifetime of 2-methoxyestradiol while retaining the desired anti-angiogenic and anti-tumor activity. *See* specification, page 11, lines 16-27. Indeed, initial screening of epimeric 16-ethyl-2-methoxyestradiol and related analogues showed that it is about equipotent to 2-methoxyestradiol in inhibition of HUVEC cell proliferation *in vitro*. *See* specification, page 17, lines 2-6.

Further, Applicants respectfully maintain that the specification (page 20, lines 20-25; Examples 23 and 24, pages 31-34) provides at least three (3) different assays that are useful in determining and predicting the antiproliferative and antitumor activity of the compounds, namely the $IC_{50}$ values in HUVEC cells, the $IC_{50}$ values in MDA-MB-231 cells, and the Proliferation Index in estrogen dependant MCF-7 cells. The specification further indicates that all of these compounds exhibited antiproliferative or antiangiogenic activity in at least one of the assays.

Applicants further assert that *additional* assays are disclosed in the specification that are useful in determining and predicting the antiangiogenic activity of the compounds. For example, the specification discloses the chick embryo chorioallantoic membrane (CAM) assay as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention. *See* specification, page 12, lines 1-17. Pharmaceutical formulations and dosages of the compounds are also disclosed. *See* for example, specification page 17, line 8-page 19, line 20.

Accordingly, Applicants respectfully maintain that the specification has clearly delineated a basis for selecting species that exhibit and are expected to inhibit angiogenesis. Accordingly, Applicants respectfully maintain that *In re Dreschfield* provides no basis for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled.

c. *Sufficient Number of Representative Examples.* The Examiner states that the disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds within the scope of a claim will possess the alleged activity. The Examiner further states that "predicting the activity of all the estradiol derivatives as in Claims 10 and 19 is impossible."

Applicants respectfully submit that numerous representative examples have been provided in Examples 1-24, including Table 2, which provide reasonable assurance that the

compounds of the present invention will possess the desired activity. Table 2 of the specification discloses numerous 16-substituted 2-methoxyestradiol compounds of the present invention, along with data regarding their antiproliferative, antiangiogenic, and antitumor activity. *See* Example 24, page 33; Claims 11-18. Both HUVAC (Example 24) and MDA-MB-231 (Example 23) *in vitro* cellular proliferation inhibition assays are disclosed in the specification as means to test the compounds according to the present invention. *See* specification, pages 31-34. The specification further discloses the chick embryo chorioallantoic membrane (CAM) assay as a suitable assay for angiogenesis inhibiting activity for compounds of the present invention. *See* specification, page 12, lines 1-17. Pharmaceutical formulations and dosages of the compounds are also disclosed. *See* for example, specification page 17, line 8-page 19, line 20.

Applicants maintain that the specification discloses numerous representative examples which provide more than reasonable assurance to one skilled in the art that the compounds within the scope of the claims possess the desired activity. The specification also provides standard tests for screening and identification of the claimed compounds that exhibit angiogenesis inhibiting activity, along with pharmaceutical formulations and dosages of the compounds. Therefore, Applicants respectfully submit that the Examiner's assertion is incorrect and provides no ground for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph as being non-enabled.

4. The Presence or Absence of Working Examples. The Examiner states, that there is no data for compounds having a variety of substituents at the 1-, 2-, 3-, 4-, 6-, 16-, or 17-carbons that would assist the skilled artisan in practicing the claimed invention. The Examiner states that the skilled artisan would be at a loss as to where to begin such discovery in the absence of such data. Applicants submit that the examiner's argument is now moot because all claims are only modified at the 16-position and that Table 2 of the specification discloses several

working examples of 16-substituted 2-methoxyestradiol compounds of the present invention, along with data regarding their antiproliferative and antiangiogenic activity. *See* Example 24, page 33; Claims 11-18.

Therefore, Applicants respectfully maintain that the Examiner's assertion of lack of data is incorrect, and does not constitute a ground for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph.

5. The Breadth of the Claims. It is the Examiner's position, as set forth in the Office Action, that the claims of the present invention are drawn to a method of treating angiogenesis using hundreds of compounds as provided in Claims 10 and 19, therefore these claims are considered broad. Applicant submit that this portion of the examiner's argument is now moot in view of the foregoing amendment of the claims.

The Applicants respectfully assert that the scope of the *enablement* provided by the disclosure is *commensurate with the scope of the protection sought* by the claims. *See* MPEP § 2164.08; *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). Accordingly, claim breadth is itself an insufficient ground for rejecting Claims 10-30 under 35 U.S.C. § 112, first paragraph as being non-enabled. *See* MPEP § 2164.08.

Accordingly, Applicants maintain that the scope of the enablement in the disclosure is *fully commensurate* with the scope of the protection sought by the claims, and respectfully assert that the Examiner's assertion of claim breadth does not provide a proper basis for rejecting Claims 12-18 and 39 under 35 U.S.C. § 112, first paragraph as being non-enabled.

6. The Quantity of Experimentation Needed. It is the Examiner's position that: *i)* the nature of the method claimed is so unpredictable; *ii)* the claims are drawn to a broad range of pharmaceuticals for treating angiogenesis; and *iii)* there is a general lack of guidance present in the specification, that the skilled artisan would require undue experimentation to practice the

claimed invention. In particular, the Examiner states that the biological activity of an estradiol derivative cannot be predicted *a priori*, but must be determined case-by-case by resorting to an undue, "painstaking experimental study", to determine if the estradiol derivative shows angiogenesis activity. Respectfully, Applicants traverse this statement for the following reasons.

Applicants respectfully submit that at the time of their invention, one of ordinary skill in the art could readily practice Applicants' invention without undue experimentation. Applicants submit that enablement is not precluded by the necessity for some experimentation, such as routine screening. *John Hopkins Unvi. v. CellPro, Inc.*, 152 F.3d. 1342 (Fed. Cir. 1998). "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." *Id.* at 1360. Thus, the fact that some experimentation is necessary is permissible.

Applicants invention is directed towards the treatment of angiogenesis and angiogenesis-dependent disorders, thus it was necessary to determine if a compound of Applicants' invention inhibits angiogenesis. Applicants submit that once the anti-angiogenic activity of a compound is determined, it is merely routine testing, for one of ordinary skill in the art, to examine the angiogenic inhibition of a particular disease in a suitable test model, using histological techniques. For example, it was known that proliferative retinopathy, which mimics the neovascular component of acute retinopathy of prematurity, could be developed in new born mice exposed to high (> 98%) ambient oxygen during the new born period. *See Gole et al., "The Mouse Model of Oxygen-Induced Retinopathy: A Suitable Model for Angiogenesis Research," Doc. Ophthalmol.* (1990) 74(3): 163-169. Stimulation of wound healing could be

studied in rats by repeated localized administration of brain extract from cattle containing fibroblast growth factor activity. *See Buntrock et al., "Stimulation of Wound Healing Using Brain Extact with Fibroblast Growth Factor (FGF) Activity. II. Histological and Morphometric Examination of Cells and Capillaries," Exp. Pathol.* (1982) 21(1):62-67. An experimental model was also developed to study macular degeneration. *See Ryan, S.J., "The Development of an Experimental Model of Subretinal Neovascularization in Disciform Macular Degeneration," Trans. Am. Opthalmol. Soc.* (1979) 77:707-745. Applicants incorporated by reference U.S. Patent No. 5,001,116 (see page 5, line 28) which discloses that inflammatory angiogenesis can be induced by the implantation of silica particles into a rabbit cornea, and that immune angiogenesis can be induced by the implantation of the lymph node of a different rabbit (see column 12, lines 6-9 of 5,001,116). This patent also discloses an animal model for the study of angiogenesis in tumor vessels. Moreover, since human subjects cannot be treated with new experimental drugs, the new drug must be tested on animal or *in vitro* models.

The specification also discloses the use of the chick embryo choriollantoic membrane (CAM) assay to test the compounds of Applicants' invention. *See* specification, page 12, lines 1-17. This assay, a standard screening test to determine anti-angiogenic activity, was known in the art at the time of Applicants' invention. *See Folkman, J. et al.,* Angiogenesis," *J. Biol. Chem.* (1992) 276(16), page 10932. Although the assay was implemented with only one representative compound, 2-methoxyestradiol, the assay serves as the test for all of the compounds of Applicants' invention, including the 16-substituted 2-methoxyestradiol compounds.

The extensive experimental data showing the anti-angiogenic activity of compounds disclosed in this invention, using HUVEC cells (*See* Example 24) and MDA-MB-231 cells (*See* Example 23) and proliferation index in estrogen dependant MCF-7 cells, supports

the use of 16-substituted 2-methoxyestradiol derivatives as an anti-angiogenic agent, in accordance with the disclosure in the specification. Thus, Applicants respectfully submit that the specification is fully enabled. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

**Conclusion:**

In view of the foregoing amendments and remarks, Applicants respectfully maintain that Claims 12-18 and 39 are fully enabled and hence are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404-745-2408 is respectfully solicited.

Respectfully submitted,

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